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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,436	12/22/2004	Hilde Azjin	TIP0015 US	7541

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PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,436	AZJIN ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2 September 2009 has been entered.

DETAILED ACTION

This Office Action is in response to the amendment filed 2 September 2009. Claims 1-4 have been cancelled. Claim 5 is pending and currently examined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claim 5 under 35 U.S.C. §103(a) as being obvious over Stein *et al.* (1994, hereinafter "Stein") in view of Servais *et al.* (10 March 2001, GenBank Accession Number CAB86592, GI:7529531, hereinafter "Servais") and Kim *et al.* (2001, hereinafter "Kim") is **maintained** for reasons of record.

The instant claim is directed to a method for evaluating a change in susceptibility of a reverse transcriptase inhibitor (RTI) for a second anti-HIV therapy comprising:

(i) receiving a sample from an HIV-infected patient who has been treated with a first anti-HIV therapy;

(ii) determining whether said sample from said HIV-infected patient comprises an HIV reverse transcriptase having a mutation at the position 194 from the wild type amino acid glutamate to glycine (E194G) as compared to the wild-type HIV strain IIIB/LAI;

(iii) introducing said RTI for said second anti-HIV therapy to said sample from said HIV-infected patient containing said mutation;

(iv) determining the susceptibility of said HIV having said reverse transcriptase mutation of step (ii) to said RTI in said sample;

(v) comparing the anti-HIV drug effectiveness in said sample containing said reverse transcriptase mutation with a sample not containing such said mutation; and

(vi) correlating the presence of said reverse transcriptase mutation of step (ii) to a change in the susceptibility of said RTI.

Stein discloses receiving a sample from an HIV-infected patient and determining whether the sample comprises a nucleic acid encoding HIV reverse transcriptase having a mutation at position 194 from wild type amino acid glutamate (Glu or E) (page 216, Table I); and correlating the presence of the mutation to a change in effectiveness or susceptibility of a nucleoside reverse transcriptase inhibitor (RTI), azidothymidine (AZT) (page 117 and Table II).

Stein does not disclose the specific amino acid change to glycine (G) at position 194 (E194G) or evaluating the effectiveness of a second HIV RTI for a pre-treated patient.

According to the GenBank sequence GI:7529531, Servais discloses the E194G mutation in the reverse transcriptase in samples from patients who have been treated with a first anti-HIV therapy containing RTIs zidovudine and zalcitabine.

Stein and Servais do not expressly suggest introducing a second therapy RTI to a pre-treated patient sample containing the drug-resistant mutation(s).

However, Kim discloses a method of introducing HIV nucleoside reverse transcriptase inhibitor, 3'-fluoro-3'-deoxythymidine (FLT), to both a wild-type HIV-1 isolate and multidrug-resistant HIV-1 patient isolates containing known mutations. The activity of FLT against the patient isolates are determined by drug susceptibility assays and compared to the activity against the wild-type isolate (Abstract). The FLT would be

a second anti-HIV therapy for the patients because the multi-drug resistant HIV-1 isolates are obtained from the patients who have already been treated with a first therapy.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the drug-resistance mutation profiles taught by Stein and Servais because both evaluation methods use the same RTI, AZT, and to modify the evaluation method of Stein to further include the steps for evaluating a second therapy RTI as suggested by Kim. One having ordinary skill in the art would have been motivated to do this so that the E194G mutation contributes to a more complete and accurate drug evaluation for any novel HIV RTIs while the in vitro test of introducing a RTI to a pre-treated patient sample containing the known RTI-resistant mutation(s), as a result of the first anti-HIV therapy, helps identify more potent RTIs in a rapid assay. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments have been fully considered but are not persuasive. Applicant argues that none of the references suggest the correlation of the HIV reverse transcriptase (RT) mutation E194G to a change in susceptibility or resistance of a HIV strain to a second anti-HIV reverse transcriptase inhibitor (RTI). Examiner does not concur. The cited prior art, Stein, Servais and Kim, when viewed as a whole, render the current invention obvious to one of ordinary skill in the art. As set forth in previous

Office Actions, Stein discloses the E194 mutation in correlation with a change in susceptibility to RT inhibitors, while Servais discloses the E194G mutation in a patient treated with a first HIV therapy, nucleoside RTI. Kim suggests introducing a second therapy to patient isolates with inhibitor-resistant mutations, which resulted from treatment with a first RTI, and testing susceptibility of the second RTI by screening for mutations and correlating with resistance to the second therapy. The Kim reference therefore discloses the claimed second therapy with an RTI. Therefore, the 103 rejection is maintained for reasons of record.

Applicant argues that neither the Servais nor Kim reference discloses determining susceptibility of HIV with the RT mutation E194G to a second anti-HIV therapy. Applicant's assertion seems to be requiring all the claim limitations be disclosed in a single reference. However, there is no such standard for the obviousness analysis. Examiner's rationale for the obviousness analysis is re-iterated here for clarity: Stein directs one of ordinary skill in the art to HIV RT position E194 to determine mutation in correlation with a change in susceptibility of a first therapy RTI; Servais clearly identifies HIV RT mutation E194G in correlation with the susceptibility of an RTI; and Kim discloses introducing a second RTI to an HIV patient isolate and determining RT mutations and correlating with the susceptibility of the second therapy RTI. All three references disclose the step of correlating RT mutations with the susceptibility of an RTI, which is the nexus for obviousness when the three references are combined and viewed as a whole. Kim's teaching would motivate a skilled person to make the

combination with all prior art teachings of RTI-susceptibility-correlated HIV RT mutations. Furthermore, one skilled in the art would at once envisage the RT mutation E194G that has been correlated with RTI susceptibility, whether the RTI is a first or a second therapy.

Multiple references in the prior art can be combined to show that a claim is obvious. Any need or problem known in the field and addressed by the patent can provide a reason for combining the elements in the manner claimed. A step in the obviousness analysis is to "determine whether there was an apparent reason to combine the known elements in the fashion claimed." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398,418 (2007). A rejection for obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion." Id., quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The proper question to ask is whether a person of ordinary skill in the art would have seen a benefit to combining the prior art teachings. *KSR*, 550 U.S. at 424. In this case, the claim limitations are

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according to known methods to yield predictable results: The rationale to support a conclusion that the claims would have been obvious

is that all the claimed elements (amino acid substitution of wild type residue glutamate (Glu or E) with glycine (Gly or G) at position 194 of the RT region of an HIV isolate) were known in the prior art as taught by Servais and one skilled in the art could have arrived at the claimed invention by using known methods (determining RT mutations and correlating with the susceptibility of the second therapy RTI taught by Kim) with no change in their respective functions and the combination would have yielded nothing more than the predictable results of more effective evaluation of the RTI drug susceptibility of an HIV isolate containing the specific mutation compared to the wild type HIV isolate.

B) Simple substitution of one known element for another to obtain predictable results: The rationale to support a conclusion that the claims would have been obvious is that the substitution of one known element (a first RTI therapy) with another (a second RTI therapy) would have yielded predictable results of drug susceptibility evaluation to one of ordinary skill in the art at them time of the invention.

C) Use of known technique to improve similar products in the same way: The rationale to support a conclusion that the claims would have been obvious is that a method of determining a RT mutation and correlating with the susceptibility of any RTI, was made part of ordinary capabilities (performing the same method analysis for a second RTI) of one skilled in the art based upon the teachings of Servais. One of ordinary skill in the art would have been capable of applying the known methods of determining RT mutations and correlating with the susceptibility of an RTI to improve the evaluation of

any RTI used in a first, second, or however many therapies to be used in a therapy and the results would have been predictable to one of ordinary skill in the art.

D) Applying a known technique to a known product ready for improvement to yield predictable results: The rationale to support a conclusion that the claims would have been obvious is that a particular known technique (determining RT mutations and correlating with the susceptibility of an RTI) was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying this known technique to a known product (e.g. RTI) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

E) "Obvious to try" --- choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success: The rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to pursue the known options (e.g. amino acid substitutions at position 194 of the HIV RT region) within his or her technical grasp. This leads to the anticipated success of evaluation of the susceptibility of the HIV isolate to an RTI , it is likely the product of not innovation but of ordinary skill and common sense.

F) Some teachings, suggestion, or motivation in the prior art that would have lead one of ordinary skill to modify the prior art reference to arrive at the claimed invention: Since the improvement of evaluating the susceptibility of any RTI in correlation with an amino acid substitution at position 194 of the HIV RT region would have been predictable at the time of the invention, there would have been reasonable expectation of successful

development of a second RTI evaluation method as claimed. The prior art had recognized the obstacles to be overcome in development of an RTI evaluation method with improved HIV RT mutation profiles and had suggested a finite number of amino acid substitutions including at position 194 of the HIV RT region to overcome the obstacles. The claims were obvious because it would have been obvious to try the known methods of determining amino acid substitutions at position 194 of the HIV RT region for the evaluation of a second RTI, with a reasonable expectation of success.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See *In re Rosselet*, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)

("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

In conclusion, given that the prior art teaches and claims that position 194 of the HIV RT region can be used for determining the susceptibility of an HIV isolate to an RTI, the prior art also provides multiple working examples of RTIs correlated with the amino acid substitution at position 194 of the HIV RT region, it would have been obvious to one of skill in the art at the time of the invention to achieve the predictable results of determining the susceptibility of an HIV isolate to any other RTI by determining the amino acid residue at position 194 of the HIV RT region.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648
16 September 2009

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643